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Fetal sleep organization: A biological precursor of self-regulation in childhood and adolescence?

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ABSTRACT

Fetal sleep states emerge during the third trimester of pregnancy and involve multiple interconnected neuronal networks. We examined whether fetal sleep characteristics predict child and adolescent self-regulation in a non-clinical sample (study group, $n = 25$; reference group, $n = 48$). Combined recordings of three sleep variables (fetal heart rate, body movements and rapid eye movements) were made for 2 h at 36–38 weeks' gestation. Fetuses showing synchronous change of sleep variables (i.e. within 3 min) at transition from quiet into active sleep reached a higher level of effortful control, both at 8–9 and 14–15 years, than fetuses not making synchronous transitions and compared with the reference group. Results are discussed from a Developmental Origins of Behavior, Health and Disease (DOBHAD) point of view. It is concluded that studying sleep ontogeny offers the possibility to gain insight into brain maturational processes and/or environmental adaptive processes that may have long term behavioral developmental consequences.

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1. Introduction

Research in the laboratory and clinical settings has increased the knowledge of sleep medicine (Cardinali and Pandi-Perumal, 2006). Recent literature also reveals a renewed interest in sleep–wake cycles, their precursors and biological correlates (Saper et al., 2001, 2010). From different angles sleep is a topic of interest for biological psychology, e.g. for studies of the autonomic nervous system (Lehtonen and Martin, 2004), of learning and memory (Milner et al., 2006; Fogel and Smith, 2011), and when considering its developmental origins. Several reviews focus on the ontogeny of sleep in the fetus and the preterm and full term infant, documenting how, due to developmental plasticity, sleep plays a critical role in early brain development, arousal regulation, attention, and cognition (Mirmiran et al., 2003; Peirano et al., 2003; Graven and Browne, 2008; Scher, 2008; Mulder et al., 2011).

According to Scher (2008), the study of sleep ontogeny can document patterns of brain maturation. Physiological maturity or

dysmaturity of the fetus and newborn may be the neurophysiologic expression of typical and altered developmental neural plasticity, respectively, and predict later outcome. In one study, sleep measures of both the healthy preterm infant (assessed at term equivalent age) and the healthy full-term newborn were predictive of performance on the Bayley scales of mental development at 12 and 24 months (Scher et al., 1996). In another study, in high-risk premature infants born at gestational ages from 27 to 29 weeks onwards, the degree of sleep state control after birth was associated with postnatal neurodevelopmental status at term equivalent age (Holditch-Davis and Edwards, 1998). These examples indicate that both in the absence and presence of major illness and stress, later behavioral developmental outcome is predicted by fetal and neonatal sleep state measures. These measures of brain maturation may reflect adaptation to conditions of the prenatal environment. The predictive value of these measures for behavioral developmental outcome in later life has remained unexplored due to lacking long-term follow-up studies. Therefore, in our study we examine, in a non-clinical sample, whether differences in sleep state organization in the near term fetus, may account for differences in child and adolescent self-regulation.

This study is relevant in the light of the developmental origins of health and disease (DOHAD) concept (Barker, 1998; Gluckman and Hanson, 2004; Seckl and Holmes, 2007), and the concept of

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developmental origins of behavior, health and disease (DOBHAd) in particular. The latter explicitly integrates brain–behavior relationships. The processes studied encompass variations in both typical and atypical developmental and maturational patterns (Raikkönen et al., 2011; Van den Bergh, 2011a,b,c), which are seen as adaptation to the environment resulting from gene–environment interaction (Gottlieb, 1997). They may predict behavioral development, brain–behavior relationships and health or disease expressed later in human life (Scher, 2008; Gluckman et al., 2010; Van den Bergh, 1990, 1992, 2011c).

Fetal behavioral states, also called sleep states, emerge during the third trimester of pregnancy and involve multiple interconnected neuronal networks. Functional (re)organization of sleep cycling likely occurs around 28–30 weeks postmenstrual age (PMA), 36 weeks PMA, and 48 weeks PMA (i.e. 2 months after birth) (Visser et al., 1987; Nijhuis et al., 1999; Scher, 2008). From 36 weeks' gestation onward, the low-risk fetus exhibits two states of sleep and two states of wakefulness. Each state is defined by a specific combination of three state variables: fetal heart rate pattern (HRP A through HRP D), absence or presence of fetal generalized body movements (GM) and absence or presence of rapid eye movements (REM) (Nijhuis et al., 1982; Mulder et al., 1987). Fetuses normally pass through sleep cycles of non-REM (quiet) sleep and REM (active) sleep, which last about 70–90 min (Visser et al., 1992). The time spent in wakefulness is usually less than 10%. Typical fetal sleep states show concordant (uninterrupted) association between the state parameters for prolonged time, and simultaneous (synchronized) change of state parameters (≤ 3 min) at their beginning and end (transitions). The degree of sleep state stability and the duration of transitions into and out of a particular state are considered measures of neurophysiological development, integrity and maturity (Visser et al., 1992; Mulder et al., 1998).

Theories of self-regulation presume that human beings, from prenatal life or birth onward, display individual differences in behavioral reactivity and regulation that have implications for subsequent development and adaptation (Kopp, 1982, 2003; Calkins and Fox, 2002; Posner and Rothbart, 2000; Gunnar et al., 2009; Pruessner et al., 2010). Reactivity is understood as the arousability of physiological and behavioral systems, while self-regulation refers to neural and behavioral processes which function to modulate this reactivity. Individual differences in reactivity and regulation are thought to be constitutionally based and influenced over time by the continuous interaction between genetic factors, maturation, and experience (Rothbart and Derryberry, 1981; Rothbart and Bates, 1998; Rothbart et al., 2001; Van den Bergh, 2011c). As the child grows older, initial reactive forms of regulation are supplemented by an increasing capacity for volitional or effortful control (Derryberry and Rothbart, 1997). Much of the self-regulation development results from increasing volitional control over attentional processes and enhanced inhibitory control over motor behavior (Calkins and Fox, 2002). Starting in childhood and continuing throughout adolescence, executive functions such as attentional focusing, maintenance and shift of focusing, and inhibitory control become integrated in complex emotional and behavioral regulatory processes. These processes, in turn, are involved in planning and goal setting, responsible decision making, emotional and motivational changes, and interpersonal relationships (Rothbart and Bates, 1998; Nelson et al., 2002).

In sum, presently there is no empirical work on individual differences in typical fetal brain maturation processes, such as expressed in sleep organization, in relation to their long-term consequences for self-regulation. Therefore, the aim of this prospective longitudinal study is to examine which measures of sleep organization in the normal near-term fetus are predictors – and hence precursors – of measures of self-regulation obtained from the same individuals when 8–9 and 14–15 years of age.

2. Materials and methods

2.1. Participants

The present study is part of a long-term prospective project that was approved by the Institutional Review Board of the Katholieke Universiteit Leuven, Belgium. At the beginning of the project, 86 healthy pregnant women were enrolled at 12–22 weeks of gestation (all participants gave their informed consent). They fulfilled the following criteria: singleton pregnancy, nulliparity, clean medical history and low obstetrical risk, Dutch-speaking, Caucasian, 18–30 years old, and no use of medication or drugs. All pregnancies were dated using the last menstrual period and/or an ultrasonographic examination before 14 weeks. Socio-demographic and obstetrical data were collected by interview and medical chart review. Our sample consisted mainly of married women (94%). The course of pregnancy remained unremarkable for all women and hospital delivery between 36 and 41 weeks of gestation was uneventful. All infants were born at term, except for four infants, two in the reference group and two in the study group (see below), who were born between 36.0 and 37.0 weeks' gestation (late preterm infants). All infants were appropriate-for-dates (birth weight above the 10th percentile) and born in good condition (5-min Apgar scores 9 or 10); no postnatal medical complications occurred, including seizures, head trauma or central nervous system infections (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005, 2006; Mennes et al., 2006, 2009).

Thirteen out of the 86 initially included mother–fetus pairs were lost to follow-up in the current investigation. Our study group comprised 25 women who participated both in a fetal behavioral observation session at the end of pregnancy and in the follow-up study on their offspring. The reference group consisted of 48 mothers and their children/adolescents who did participate in the follow-up study but not in the fetal observation study. For the follow-up study reported here, the mothers completed a temperament questionnaire when their children were 8–9 years ($n=62$) and 14–15 years ($n=65$) old (see below).

2.2. Fetal assessment protocol and measures of fetal behavioral state organization

Simultaneous recordings of fetal heart rate (FHR), fetal generalized body movements (GM), and fetal rapid eye movements (REM) were made for 2 h continuously at 36–38 weeks' gestation. The fetal recordings were performed with the mother resting in a semi-recumbent position in a quiet room at University Hospital Gasthuisberg in Leuven, Belgium. Recording took place between 2 and 6 pm, starting at least 1.5 h after lunch to control for potential diurnal influences and effects of maternal food intake (Mulder et al., 2010).

FHR was monitored with a cardiotocograph by means of Doppler ultrasound and recorded at a paper speed of 3 cm/min (Hewlett Packard 8040A, Böblingen, Germany).

The FHR tracings were judged visually and divided into episodes of heart rate pattern (HRP) A, B, C or D (see below) by an independent experienced researcher as previously described (Nijhuis et al., 1982; Mulder et al., 1987).

Fetal generalized body and eye movements were identified by two observers each using a linear-array real-time ultrasound scanner. The images of both devices were videotaped and the tapes were marked at the beginning and end of recording for synchronization with each other and with the FHR tracing. The presence of GM and REM was marked on-line with hand-held pushbuttons by the observer who held the first and second transducer, respectively. Fetal REM were recorded as event, but for each GM the button was pressed as long as the movement was observed. GM were defined as all fetal trunk movements, including startles. After synchronization, all information on occurrence and duration of fetal movements and HRPs was stored in a personal computer for off-line analysis (Van den Bergh, 1989).

The presence of each of four distinct behavioral states (S1F–S4F) was identified according to predefined criteria using a well-established procedure (Nijhuis et al., 1982; Mulder et al., 2011). The temporal association between HRP, GM, and REM was determined from presence-absence profiles drawn up for each state variable separately using the 3-min moving window technique (Nijhuis et al., 1982; Mulder et al., 1987). Episodes of state 1F (S1F; quiet or non-REM sleep) are defined by a stable heart rate with a small oscillation bandwidth (HRP A) and absence of general and eye movements. During state 2F (S2F; active or REM sleep), general and eye movements are present and heart rate has a wide oscillation bandwidth between the frequent accelerations (HRP B). During state 3F (S3F; quiet awake), general movements are absent and eye movements present; the heart rate pattern is stable and without accelerations (HRP C). Characteristic for state 4F (S4F) episodes (active awake) are frequent vigorous general movements in the presence of eye movements, and an unstable heart rate pattern with large accelerations (HRP D).

An episode for which none of the specified combinations was applicable was classified as 'no-state identified' (NoS) when bounded at either side by the same state, or as transition when bounded by two different states. The incidences of states 1F–4F and NoS were expressed as percentage of recording time. For each recording, the number and duration of all state transitions were determined. For the transitions from state 1F into state 2F and vice versa, distinction was made between synchronized transitions, defined by duration of ≤ 3 min, and non-synchronized transitions (duration > 3 min). The duration of transitions from state 1F into state 2F and vice versa were analysed separately, because it cannot be assumed that transitions in either direction express the same degree of functional integrity and maturity of the

Table 1

Characteristics of synchronized and non-synchronized fetal state transitions among fetal behavior recordings in the study group ($n = 25$). Data are presented as mean, standard deviation (SD) and range, or as number (%).

	Transitions from S1F into S2F		Transitions from S2F into S1F	
	Synchronized ($n = 15$)	Non-synchronized ($n = 10$)	Synchronized ($n = 13$)	Non-synchronized ($n = 12$)
Transition duration (s)	83 (27); 40–125	286 (54); 189–374**	120 (40); 40–170	271 (69); 190–435**
Duration TranS1F–2F (s)			145 (104); 50–374	190 (115); 40–344 n.s.
Synchronized TranS1F–2F (n , %)			10 (77%)	5 (42%) n.s.
Duration TranS2F–1F (s)	163 (79); 40–303	240 (100); 105–435*		
Synchronized TranS2F–1F (n , %)	10 (67%)	3 (30%) n.s.		

Student's t -test for independent samples or Fisher exact test.

* $p < 0.05$.

** $p < 0.0001$.

CNS (Groome et al., 1996). For instance, transitions from state 1F into state 2F have been shown to exhibit earlier synchronization than transitions from state 2F into state 1F (Nijhuis et al., 1999).

2.3. Maternal report of self-regulation (effortful control) in childhood/adolescence

Mothers were asked to fill out widely-used temperament questionnaires when their children were 8–9 and 14–15 years old. We used the Dutch versions of the *Children's Behavior Questionnaire* (CBQ; Ahadi et al., 1993) and the revised *Early Adolescence Temperament Questionnaire* (EATQ-R; Capaldi and Rothbart, 1992; Ellis and Rothbart, 2001) which show good psychometric qualities and have been translated by us (Van den Bergh and Ackx, 2003) or others (Hartman et al., 2002), respectively.

At 8–9 years, the CBQ was used, a temperament scale consisting of 18 scales with 12–14 items each. In both the original and translated versions, extraversion/surgency, negative affectivity, and effortful control were second order factors in a principal-component factor analysis performed on 15 of the 18 subscales (Van den Bergh and Ackx, 2003). Effortful control was defined by four scales. For each scale, Cronbach's alpha and the loading on effortful control are presented (in brackets) as well as a sample item: (1) low intensity pleasure (.55/.84): "Doesn't care much for quiet games (reverse)"; (2) inhibitory control (.82/.71): "Can lower his/her voice when asked to do so"; (3) perceptual sensitivity (.71/.68): "Is quickly aware of some new item in the living room"; and (4) attentional focusing (.87/.57): "When practicing an activity, has a hard time keeping his/her mind on it".

At 14–15 years, we used the EATQ-R designed to assess aspects of temperament related to self-regulation in 9–16 year-old children (Capaldi and Rothbart, 1992; Ellis and Rothbart, 2001). The EATQ-R (short form) consists of 10 scales each containing 5–9 items, 62 items in total. Items are scored from 1 to 5 with a higher score reflecting a higher degree of the dimension measured. A principal-component factor analysis with communalities estimated through iteration was used to identify the latent structure. Three second order factors were revealed in our sample: surgency (or positive reactivity), negative affectivity, and effortful control. Effortful control was defined by three factors. For each scale, Cronbach's alpha and the loading on effortful control are presented (in brackets) as well as a sample item: (1) Attention (.78/.87): "Has a difficult time tuning out background noise and concentrating when trying to study (reverse)"; (2) Inhibitory Control (.64/.85): "Has a hard time waiting his/her turn to speak when excited (reverse)"; (3) Activation Control (.81/.84): "Usually gets started right away on difficult assignments".

The standardized factor score for effortful control (Z -score) was taken at both ages as a measure of self-regulation; the Z -scores are comparable across ages.

2.4. Confounders

The following potential confounders were included: maternal age; educational level (coded on a 3-point scale); smoking and alcohol use during the first trimester of pregnancy (yes/no); and neonatal birth weight and 5-min Apgar score.

2.5. Statistical analysis

SPSS for Mac (version 18, SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Variables not normally distributed were included as their natural log n . Results were summarized with the use of standard descriptive statistics: counts and percentages for categorical variables, and means and SD or SE for continuous variables. Groups were evaluated for equivalence in characteristics using the Fisher exact test for categorical measures, and (un)paired t -tests for continuous variables. Pearson correlation coefficients were determined for bivariate relationships. Linear mixed model (multilevel) analysis was performed to explore differences in effortful control on the two postnatal test ages across the three antenatal groups. This procedure allows for inclusion of individuals with missing data on one test occasion. Test age was introduced at level 1 and nested within the individuals (level 2). The predicted test scores were subsequently subjected to one-way ANOVA and post hoc t -tests to examine group differences. With all tests, significance was assumed at $p < 0.05$.

3. Results

3.1. Sleep state organization in the near term fetus (study group)

Mean gestational age at fetal recording was 36.4 weeks (SD 0.5; range 35.8–37.6 weeks) and the recordings lasted 110 min on average (SD 16; range 62–125 min). Only 1 and 6 fetuses spent time in S3F (4%) and S4F (range 2–13%), respectively. Because of low occurrence, S3F and S4F were not considered further. The mean incidences of state 1F, state 2F, and NoS were 27% (SD 12%; range 7–58%), 48% (SD 13%; range 16–67%), and 16% (SD 12%; range 0–56%), respectively. The mean durations of all transitions from S1F into S2F (TranS1F–2F) and those from S2F into S1F (TranS2F–1F) were 164 s (SD 109; range 40–374 s) and 195 s (SD 95; range 40–435 s), respectively, and not statistically different ($p = 0.30$). Fetuses showing synchronous TranS1F–2F (i.e. ≤ 3 min) had also shorter S2F into S1F transitions compared with fetuses without synchronous TranS1F–2F (Table 1). This was not found for TranS2F–1F (Table 1). Gestational age at recording and that at delivery did not differ statistically between fetuses with and without synchronous TranS1F–2F (p -values 0.93 and 0.79, respectively).

3.2. Maternal and child measures

The reference and study groups did not differ for main socio-demographic, obstetrical/neonatal, and child/adolescent psychological variables (Table 2). The standardized scores on effortful control for all children (8–9 years; $n = 62$) and adolescents (14–15 years; $n = 65$) ranged from -1.85 to 1.93 and from -2.86 to 1.89 , respectively (mean = 0, SD = 1). There was no difference in Z -score between the reference and study groups at either age (Table 2). The Z -scores of individuals assessed on both test occasions were fairly correlated ($R = 0.53$; $p < 0.0001$; $n = 54$) and not statistically different ($p = 0.81$; paired t -test).

3.3. Relationships between potential maternal/fetal confounders, prenatal predictors, and effortful control (dependent variable)

An overview of bivariate correlations between predictor, confounding, and dependent variables is presented in Table 3 (prenatal study group) and 4 (total group). Gestational age at recording and maternal age, education, smoking, and alcohol use were tested for their impact on the distinct fetal state parameters, but no factor was significantly correlated with the percent incidences of states or duration of transitions (Table 3). Synchronized TranS1F–2F were positively associated with effortful control at both postnatal test ages (Table 3). Potential confounders for effortful control relating to the total study sample are shown in Table 4.

Table 2
Demographic/obstetrical and child psychological characteristics of the reference and study groups. Data are presented as mean and standard deviation or as number (%).

	Reference group (n = 48)	Study group (n = 25)	p [*]
Maternal age [#]	26.0 (2.5)	25.5 (2.8)	.45
Maternal educational level (n, %) [#]			.17
Primary/lower secondary school	14 (29%)	7 (28%)	
Secondary school	12 (25%)	2 (8%)	
College/academic degree	22 (46%)	16 (64%)	
Smoking, yes; n (%) [#]	8 (17%)	3 (12%)	.76
Alcohol use, yes; n (%) [#]	6 (13%)	5 (20%)	.40
Gestational age at birth (wk)	38.7 (2.1)	39.3 (1.4)	.17
Birth weight (g)	3247 (564)	3269 (418)	.86
5-min Apgar score	9.5 (1.1)	9.7 (0.6)	.48
Effortful control; 8–9 year (Z-score)	−0.08 (0.96)	0.14 (0.92)	.39
Effortful control; 14–15 year (Z-score)	−0.16 (0.97)	0.23 (1.02)	.12

^{*} Student's *t*-test for independent samples or Chi-square (Fisher exact) test where appropriate.
[#] During first trimester of pregnancy.

Table 3
Pearson correlations between potential maternal confounders, fetal sleep state parameters (predictors), and children's effortful control (dependent variable) in the prenatal study group (n = 25).

	Maternal age	Education	Alcohol	Smoking	Gestational age at recording (weeks PMA)	Effortful control at 8–9 year	Effortful control at 14–15 year
State 1F (%) [†]	−.13	−.25	−.01	.24	−.12	.06	−.03
State 2F (%) [†]	.29	.12	.19	−.23	.15	−.13	.15
No-coincidence (%) [†]	−.18	−.01	−.08	.13	.05	.01	.04
Duration TranS1F-2F (s) [†]	−.10	.33	.08	.33	.10	−.48**	−.49**
Synchronized TranS1F-2F	.22	.28	−.01	−.31	.02	.49**	.47**
Duration TranS2F-1F (s) [†]	.02	−.02	.01	.12	−.15	−.16	.28
Synchronized TranS2F-1F	−.06	.09	.10	−.01	.06	−.25	.20

** *p* < 0.01.
[†] Natural log transformation.

Table 4
Pearson correlations between potential maternal/neonatal confounders and effortful control in children and adolescents (dependent variables) in the total study sample (range of n, 62–73).

	(1)	(2)	(3)	(4)	(5)	(6)	Effortful control at 8–9 years	Effortful control at 14–15 years
Maternal age [#] (1)							.06	.01
Education [#] (2)	.39***						.34**	.25
Smoking [#] (3)	.01	.06					−.01	−.13
Alcohol [#] (4)	.31**	.22	.28*				.11	.10
Birth weight (5)	.06	.08	−.12	−.14			−.03	.04
Gestation at birth (6)	−.07	.05	.02	−.03	.60***		−.08	−.03
5-min Apgar score (7)	−.05	−.11	−.03	−.11	.21	.47***	−.02	.06

* *p* < 0.05.
** *p* < 0.01.
*** *p* < 0.001.
[#] During first trimester of pregnancy.

3.4. Main analysis

Multilevel analyses were conducted stepwise using postnatal test age (fixed and random factor at level 1), maternal education (fixed factor at level 2), and study/reference group category (fixed factor at level 2) to predict effortful control at 8–9 and 14–15 years of age. There were no significant interactions between level 1 and level 2 factors. Estimates of the final model are presented in Table 5 and, after post hoc analysis at each test age, the results are graphically shown in Fig. 1. Effortful control did not change statistically among individuals from childhood to adolescence (Time effect n.s.; Table 5). After controlling for a negative effect of low education (*P* < 0.05), effortful control was similar between individuals of the reference group and those who had non-synchronized TranS1F-2F when in utero. However, children who as a fetus showed synchronized TranS1F-2F had higher effortful control scores than individuals of the two other categories (Table 5). This factor explained 21.4% of the variability in effortful control at both postnatal ages after controlling for maternal education.

4. Discussion

The present study examined whether measures of state organization in the near-term fetus are predictive of child and adolescent self-regulation. Our results show that the time a typically

Table 5
Multilevel model estimates and their level of significance for effortful control.

Factor	β	SE	p
Intercept	.05	.17	.78
Postnatal test age (Time)	−.02	.13	.87
Maternal educational level			.081
Primary/lower secondary school	−.49	.22	.029
Secondary school	−.28	.27	.29
College/academic degree	0	0	–
Study/reference group category			.004
Synchronized TranS1F-2F	.74	.24	.003
Non-synchronized TranS1F-2F	−.25	.28	.38
Reference group	0	0	–

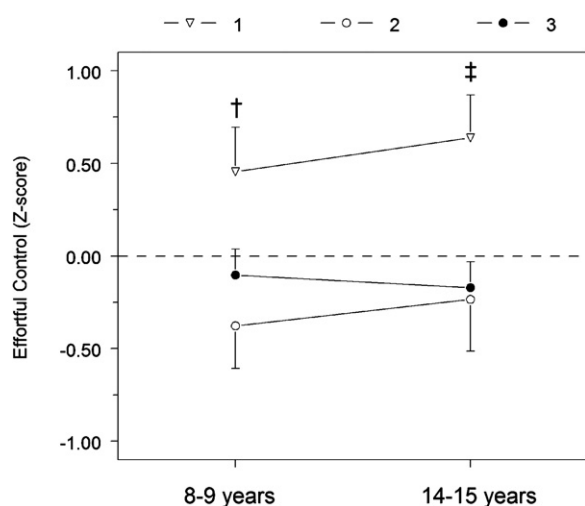


Fig. 1. Effortful control in children and adolescents in a subgroup of individuals who had synchronized transitions from State 1F into State 2F when in utero (category 1), in a subgroup of individuals who had non-synchronized transitions from State 1F into State 2F when in utero (category 2), and in the reference group (category 3). Data are presented as mean and SE. For category 1, effortful control was higher than for categories 2 and 3, respectively, at both test ages, while the two latter categories did not differ statistically. † 1-way ANOVA post hoc testing with multiple t-test comparisons at 8–9 years of age; $p < 0.01$; ‡ 1-way ANOVA post hoc testing with multiple t-test comparisons at 14–15 years of age; $p < 0.01$.

developing (normal) fetus takes to pass from quiet sleep (S1F) to active sleep (S2F) in the last month before birth is associated with its degree of self-regulation in childhood and adolescence. In particular, fetuses exhibiting sharp synchronous transitions from quiet sleep into active sleep compared with fetuses showing non-synchronized transitions (lasting >3 min) reached a higher level of effortful control (i.e. significantly higher than the reference group but within normal ranges) both at 8–9 years and 14–15 years. The duration of transitions in the opposite direction (i.e. from active sleep into quiet sleep) and the percentage of time spent in indeterminate state were not statistically associated with the degree of self-regulation in later life. We discuss possible underlying mechanisms and the relevance of our results from a DOBHaD perspective.

The mechanism underlying fetal state alternation is unknown, but may be congruent with the sleep switch (flip-flop) model recently proposed for adult REM/nonREM sleep cycling (Lu et al., 2006; Saper et al., 2010). In this model, either sleep state is controlled by a particular constellation of neurons in pontine, mesencephalic, and hypothalamic centres involving specific neurotransmitters. Both state maintenance and transitions into and out of a particular sleep state result from extensive reciprocal interactions between the two neural constellations. This intricate web of interactions may emerge well before birth enabling homeostatic cyclic processes in the immature brain (Scher, 2008). Fetal state organization presumably represents a simple though already well-regulated stage of the network. In our study, fetal recordings were made between 36 and 38 PMA (mean 36.5 PMA), a fairly narrow age range. Fully developed (true) states, therefore, were not present in each fetus during observation. Consequently, the measures of fetal state organization showed wide variation which was, however, not influenced by a number of antenatal factors, such as maternal age and education, alcohol use, smoking, and gestational age. Interfetal differences in the rate of normal state development at the time of recording, which are correlated with brain maturation, may thus have played a role (Visser et al., 1987; DiPietro et al., 1996a,b; Nijhuis et al., 1999). Only TranS1F-2F appeared a predictor of effortful control in later life (Table 3). It explained a considerable amount

of the variance (21%) in effortful control at 8–9 years and 14–15 years.

Previous longitudinal research has shown that synchronized S1F into S2F transitions emerge earlier than S2F into S1F transitions (Groome et al., 1996; Nijhuis et al., 1999). The fetuses with synchronous TranS1F-2F in our study – and this group also had shorter TranS2F-1F than the group with asynchronous TranS1F-2F – probably comprise a subgroup that has more advanced CNS development before birth. This presumed expression of advanced brain maturation, in turn, was associated with better effortful control in later life. On the other hand, non-synchronized TranS1F-2F near term predicted a normal level of effortful control. However, we can conclude that even if non-synchronized TranS1F-2F at 36–38 PMA may represent a typical pattern of brain maturation and is not a clinically ominous sign, it seems to be an early, prenatal, marker of ‘non-advanced’ brain maturation as it apparently limits the degree of self-regulation that will be reached in childhood and adolescence.

The %NoS and TranS2F-1F were not sensitive markers for self-regulation later in life. The amount of indeterminate sleep (%NoS) was rather low, indicating high stability during an on-going sleep state. It also showed small variation among recordings, which may explain why %NoS is not a precursor for postnatal self-regulation. However, at transition from active into quiet sleep (TranS2F-1F), inhibition of REM, GM, and HRP B did often not occur simultaneously in quite a number of fetuses at 36–38 weeks PMA. The achievement of synchronized TranS2F-1F, in contrast to synchronized TranS1F-2F, may be more dependent upon maturation, in line with previous observations (Groome et al., 1996; Nijhuis et al., 1999). This phenomenon may relate to differential development between particular components of the presumed flip-flop sleep switch (Lu et al., 2006; Saper et al., 2010).

Our study reveals several interesting findings regarding developmental plasticity, which are relevant from a DOBHaD perspective. It is supposed that the efficiency and organization of fetal sleep states as well as self-regulation ultimately results from gene–environment interactions. The maturational processes leading to a more advanced CNS development are due to developmental plasticity processes (Gottlieb, 1997). It is supposed that reaching synchronous TranS1F-2F near term reflects a successful adaptation to the conditions of the prenatal environment. In a similar way, reaching a high degree of self-regulation in postnatal life may reflect successful adaptation to the conditions of the postnatal environment. Interestingly, our study indicates a kind of continuity in brain maturation/environmental adaptive success: the processes of reactivity and regulation are more balanced, and modulation of cognition and emotions is more efficient in children and adolescents who as fetuses showed a more advanced sleep state pattern. In the fetus, our ultrasound (behavioral) and physiological (heart rate) measurements were crucial for studying precisely-timed sleep state transitions. In the preterm and full term born infant, EEG measures of dysmature or altered sleep state expression with advancing age and their associations with early sensory cognitive development, may offer an opportunity to characterize typical and atypical developmental neural plasticity (Scher et al., 1996; Scher, 2008). This is an important aspect of the DOBHaD-hypothesis. Developmental neural plasticity processes may influence how an individual ‘behaves’ (i.e. perceives, interprets and reacts) to its environment, and also responds to situations of acute and chronic stress. These processes, in concert with physiological activity, may underlie typical behavior as well as behavioral problems (Van den Bergh, 2011a,b) and psychopathology, or more in general, mental health problems (Van den Bergh, 2011c).

Our findings may also be seen as revealing supportive evidence – though indirect – for recent explanations that persons

vary in their biological sensitivity (Boyce and Ellis, 2005; Ellis et al., 2005, 2011; Del Giudice et al., 2011) or susceptibility (Belsky and Pluess, 2009; Pluess and Belsky, 2011) to environmental influences. These theories predict that some individuals are more susceptible than others to both the adverse and beneficial effects of unsupportive and supportive environments, respectively. This is a broadening of earlier views expressed in the transactional/dual-risk model (Sameroff, 1983) and the diathesis-stress model (Monroe and Simons, 1991; Zuckerman, 1999). These models solely assume that a vulnerability factor (or diathesis, e.g. high physiological reactivity) predisposes individuals toward problematic functioning (e.g. deficient self-regulation) in the face of environmental adversity. However, they do not express ideas about beneficial effects of supportive environments. Our results raise the question whether children and adolescents with a high degree of self-regulation who as fetuses made synchronous transitions from quiet into active sleep, are more sensitive for the positive influences not only of their postnatal environment but of their prenatal environment as well.

4.1. Future perspective

Because sleep disturbance is a significant problem in the general pediatric population (Hollway and Aman, 2011; Owens, 2008) and in many adulthood diseases (Prather et al., 2009; Srinivasan et al., 2009), the study of sleep in non-clinical populations is a topic of interest. Recent literature reveals renewed interest in sleep-wake cycles, their precursors and biological correlates (Saper et al., 2010). From a DO(B)HaD – perspective some specific questions remain to be studied. In what way will the bi-directional interactions between neurobiological correlates and the supportive and/or unsupportive environment of the child and adolescent shape the self-regulation of the adult as well as the further development and ageing of the neurobiological correlates? Is sleep ontogeny related to sleep quality and health in later life?

4.2. Strengths and limitations

To the best of our knowledge, this study is the first to demonstrate, in a community sample, a link between prenatal regulatory processes and self-regulation in 8–9 and 14–15 year olds. The prospective design with a long term follow-up, the standardized biologically-based and detailed measures of fetal sleep organization can be seen as important strengths of our study. However, several limitations of the current study deserve attention. Because of the small sample size, the external validity of our results is rather low and the results may be sample-specific. Although the percentage of variance in self-regulation that was explained by one prenatal biological precursor is substantial, a large proportion of the variance remains unexplained. The time lag between the waves of our study is large. Finally, as we do not have a genetically sensitive design we cannot testify the role of heritability. Genes shared by mother and child may account for more advanced brain maturation, explaining – at least in part – the link between fetal state regulation and child and adolescent self-regulation.

In conclusion, our study demonstrates the usefulness of studying sleep ontogeny in the fetus in a non-clinical sample. It offers the possibility to gain more insight into some aspects of brain maturational processes and/or environmental adaptive processes, and their long term behavioral developmental consequences.

Conflict of interest

The authors declare that there are no conflicts of interest.

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